ISSUES IN THE ANALYSIS OF ENVIRONMENTAL ENDOCRINE DISRUPTORS

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(Pages 96-98 in *Preprints of Extended Abstracts*, Vol. 40 No. 1)

Symposia Papers Presented Before the Division of Environmental Chemistry
American Chemical Society
San Francisco, CA March 26-30, 2000

PHARMACEUTICALS IN THE ENVIRONMENT — OVERARCHING ISSUES AND CONCERNS

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Certain pharmaceutically active compounds (e.g., caffeine, aspirin, and sex steroids) have been known for over 20 years to enter the environment by a variety of routes — primarily via treated and untreated sewage effluent. Only more recently has a larger picture emerged — where it is evident that numerous drugs and personal care products from a wide spectrum of therapeutic and consumer-use classes, many having potent biochemical activity, can occur in the environment (albeit at very low concentra-tions), especially in natural surface and ground waters. The full extent, magnitude, and ramifications of their presence in the aquatic environment are largely unknown. Whether pharmaceuticals and personal care products (PPCPs) in the environment pose an exposure risk to humans or wildlife is not known. Aquatic exposures are noteworthy, however, in that they can be continuous. Nearly all ecological monitoring studies to date have been performed in Europe. While the (over)use and subsequent direct and indirect release of antibiotics and natural/synthetic steroids to the environment has generated nearly all the controversy to date regarding pharmaceuticals as pollutants, a plethora of other drug classes, bioactive metabolites and transformation products, as well as personal care products have yet to be examined. This paper summarizes a number of issues not frequently encountered in discussions of environmental toxicology and which deserve further attention and debate.

Current Knowledge Base: Much of the current knowledge regarding the occurrence, fate, and effects of PPCPs in the environment has been captured in a critical review by Daughton and Ternes (see: Daughton, C.G. and Ternes, T.A. “Pharmaceuticals and Personal Care Products

in the Environment: Agents of Subtle Change?" *Environmental Health Perspectives Supplement*, December 1999 [in press]). Excluding the antibiotic and steroid therapeutic classes, over 50 individual PPCPs or metabolites (from more than 10 broad classes of therapeutic agents or personal care products) have been identified to date in environmental samples (mainly surface and ground waters in Europe; very few activities have occurred in the U.S.). Representative classes include analgesics/anti-inflammatories, antineoplastics, antiseptics, betablockers (antihypertensives), â2-sympathomimetics (bronchodilators), lipid regulators and bioactive metabolites, musks (synthetic nitro and polycyclics; also reduced metabolites of nitro musks), psychiatric drugs, sun screen agents, and X-ray contrast media. Concentrations generally range from the low ppt- to ppb-levels (ng/L to µg/L). Most of these compounds, however, have no associated aquatic toxicity data. Some PPCPs (such as antidepressants) that do have some associated aquatic effects data have yet to be surveyed in environmental samples. Still others have great potential for profound aquatic effects but have neither the aquatic toxicological database nor any occurrence data (e.g., psychoactive agents and narcotics).

Infrequently Discussed Issues Regarding Environmental Ecotoxicology

A comprehensive examination of the world's disparate and often disjointed literature involving pharmaceuticals in the environment reveals a number of issues not frequently encountered in discussions of environmental toxicology and which deserve further attention and debate. These are outlined here.

< **Chemical Stability Not a Requirement for "Persistence":** Continuous infusion of a pollutant to the aquatic environment is the sole, minimum ingredient necessary for effecting continual, multi-generational life-cycle exposures of sensitive aquatic species. Actual structural persistence (as with DDT and other persistent organic pollutants) is not necessary as long as the pollutant is continually introduced (such as via sewage treatment plant effluent). Current criteria for establishing the importance of pollutants keyed to chemical stability as the prime measure of "persistence" may be overlooking entire classes of potential pollutants — e.g., pharmaceuticals and the bioactive ingredients in personal care products.

< **"Holistic" Risk Assessment:** PPCPs are a very large and diverse suite of potential pollutants. They rival agrochemicals in their usage rates and diversity of chemical classes. A true, "holistic" risk assessment process (especially for the aquatic environment) must take into account all bioactive compounds to which an organism is exposed. Up to now, PPCPs comprise a major class of pollutants that have been excluded from the risk assessment process. PPCPs have never been subject to any water monitoring program (whether waste or drinking) in the U.S.

< **Non-Target Toxicological Endpoints:** The modes of action of most pharmaceuticals in humans are often poorly understood. Even less understood, however, is the spectrum of possible effects on non-target receptors (e.g., side effects). Many drugs accomplish their therapeutic value in humans by mechanisms that have yet to be elucidated; drugs tend to be evaluated based on their short-term effectiveness against "surrogate endpoints" (as an example, blood

pressure or serum cholesterol), not on the basis of long-term efficacy against disease (for example in this case, heart disease). When considering ecotoxicology, these problems are magnified yet further since the effects of PPCPs on wildlife are nearly totally unknown; many of these organisms probably have metabolic pathways and potential receptors that differ from those in humans.

< **Shared Modes of Action Can Add to Risk:** While the individual concentration of a given drug in the aquatic environment might well be very low (ng-Fg/L), the combination of numerous drugs sharing the same mode of action could be significant.

< **Unknown Aspects of Non-target Dose-effects and Inter-species Toxicology:** The inverted (U-shaped) dose-response (where toxicity lessens as the dose is reduced to a certain point, below which toxicity again increases) can negate the usefulness of predicting the type or magnitude of effects at lower doses from higher doses. This is further complicated by the facts that non-target effects can vary for a given species among drugs of the same therapeutic class as well as vary among different species of the same genus for the same drug. The approach of assessing eco risk on a class-by-class or genus-by-genus basis may be untenable, and extrapolations of effects from higher concentrations may not necessarily have any relevance to what can happen at lower concentrations.

< **Multi-Drug Resistance as a Line of Defense for Aquatic Organisms:** Certain pharmaceutical compounds have the ability to inhibit the active transport system required for preventing intracellular exposure of many aquatic organisms (analogous to multi-drug transporters). Once inhibited, the lack of this system could lead to the intracellular accumulation of many toxicants. Since multi-drug transport capacity appears to be better developed in aquatic life that is routinely exposed to toxicants, organisms in more pristine areas are more vulnerable to toxic endpoints when suffering first-time exposure.

< **Subtle Effects Might Prove Significant:** Historically, toxicological endpoints of xenobiotic exposure have usually been restricted to acute, easily measured effects such as mortality and cancer. Little attention has been paid to the universe of other endpoints through which toxicants can express their action. PPCPs have the potential to exert very subtle (e.g., neurobehavioral) effects that may escape detection but which accumulate sufficiently slowly over time as to eventually result in substantive, outward change that is incorrectly attributed or rationalized as resulting from normal, natural processes or ascribed simply as being part of “natural variation”. The actual effects are not noticed in real time — only at some future point when they culminate in untoward consequences. This issue presents a major challenge to ecological risk assessment.

< **The Need to Extend Past Our Historic Focus on Conventional Pollutants:** During the last three decades, the study of environmental chemical pollution has maintained a steady fixation on conventional “priority pollutants,” including those collectively referred to as “persistent, bioaccumulative, and toxic”

pollutants (PBTs) or as “persistent organic pollutants” (POPs); the “dirty dozen” is a ubiquitous, notorious subset of these, comprising halogenated organics such as DDT and PCBs. Much of this research has added only but incrementally to our overall knowledge base of pollutants in the environment. A portion of this focus might better be diverted to understanding the scope and significance of additional bioactive, anthropogenic chemical classes that have been long ignored.

< **Research Needs:** The issue of pharmaceuticals as pollutants in the environment is a relatively new concern in this country — one that deserves attention by a wide spectrum of scientific disciplines, ranging from microbiologists (degradation/removal of PPCPs from sewage treatment plants and the environment), analytical chemists (new methods needed for monitoring), toxicologists (aquatic and human health effects), civil engineers (possible enhancement of conventional sewage treatment processes), environmental scientists (fate, transport, uptake), risk assessors (expansion of the risk assessment process to make it more holistic), and research/policy planners (redirect some of our perhaps overwrought focus away from conventional persistent industrial chemicals to gain a more complete picture of pollutants in the environment).

Notice: The U.S. Environmental Protection Agency (EPA), through its Office of Research and Development (ORD), funded this research and approved this abstract as a basis for an oral presentation. The actual presentation has not been peer reviewed by EPA.